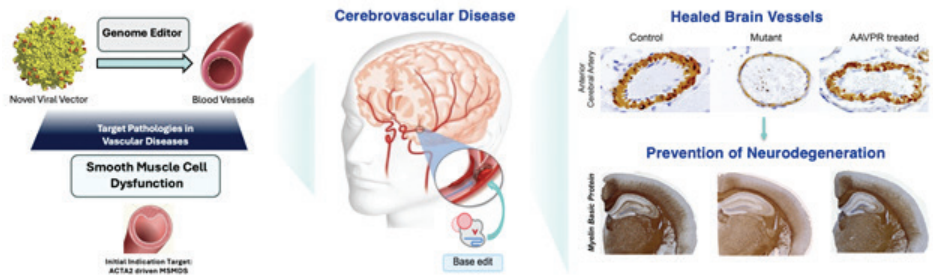

Precision Long-term Therapies for Genetic Vasculopathies that Lead to Stroke, Aortic Dissections, MI, Severe Disability, and Death in Children

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Vascular pathology underlies >80% of cardiovascular and cerebrovascular disease and remains the leading cause of death and disability in the world. Current treatments aimed to reduce vascular risk factors such as cholesterol, diabetes and blood pressure failed to timely heal already damaged blood vessels and prevent stroke, MI and aortic dissections. Genetic vasculopathies are accelerated and severe forms of vascular disease that converge on shared mechanisms of vascular damage and dysfunction with sporadic vascular disease. A major barrier to developing precision long-term therapies has been the lack of vessel-targeting therapeutic modalities.

To bridge this gap, we combined novel viral and non-viral vascular targeting delivery vehicles with genome editor engineering to correct a genetic mutation that cause one of the most severe forms of vascular disease in humans caused by mutations in the ACTA2 gene. Children born with ACTA2 driven smooth muscle dysfunction syndrome (MSMDS) experience devastating outcomes, including early-onset stroke, aortic dissection, and heart attack, typically resulting in severe disability and death before age 30. To meet the urgent clinical need of these patients, our team developed experimental models that recapitulate the human disease, a vasculotropic adeno-associated viral (AAV) vector and a BESPOKE genome editor. Our research has shown that giving this novel therapy to MSMDS mice intravenously corrects the ACTA2 mutation, normalizes vessel wall function, improves survival and prevents stroke and neurodegeneration. Additionally, we developed a complementary assay to show that the therapy is precise and effective, causing no noxious off-target effects in the treated cells.

We aim to initiate first-in-human trials in the near future as we complete ongoing IND-enabling studies. This work lays the groundwork for treating more common vascular conditions by validating next-generation gene delivery and editing platforms. By transforming therapeutic realities for children with MSDMS and related vasculopathies, our strategy opens new commercial avenues in rare disease gene therapy and accelerates breakthroughs in broader vascular medicine.